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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/696,872	10/26/2000	James E. Rothman	11746/46603	1809

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EXAMINER
SWOPE, SHERIDAN

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/696,872	ROTHMAN, JAMES E.	
	Examiner	Art Unit	
	Sheridan L. Swope	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-37* is/are rejected.

7)☒ Claim(s) *20 and 29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's cancellation of Claims 1-19 and 38-43 in Paper No. 2 is acknowledged. Claims 20-37 are pending and are hereby examined.

Specification Objection

Applicant's amendment of October 26, 2000, Paper No. 2, included numerous changes to the specification. It is requested that clean copies of the amended pages be submitted for insertion of said pages into the case.

Claim Objections

Claims 20 and 29 are objected to because of the following informalities: The construction of these claims makes the meaning somewhat unclear; it is confusing as to whether the phrase "comprising exposing the cells to a KDEL receptor inhibitor..." modifies "...the KDELr..." or "A method...". Clarity would be insured by inserting "said method" i.e. A method for promoting the release of a protein [or HSP (HSP)/antigenic peptide complex as per Claim 29] from a cell, where the protein comprises (HSP contains as per Claim 29) a ligand sequence which binds to a KDEL receptor, said method comprising exposing the cell...." Appropriate correction is required.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-37 are rejected under 35 U.S.C. 112, first paragraph. The specification is enabling for methods of increasing the secretion of a protein, or HSP/antigen complex, by a cell

wherein the protein, or HSP, comprises a KDEL receptor (KDELr) ligand selected from the group consisting of KDEL, HDEL, or SEKDEL wherein said methods use KDELr inhibitors encoded by a polynucleotide selected from the group consisting of SEQ ID NO: 14, 16, 18, 20, 22, 24, 26, 28, 30, and 35 as well as a polynucleotide encoding the proteins set forth in SEQ ID NO: 13, 15, 17, 19, 21, 23, 25, 27, 29, and 34. However, the specification does not reasonably provide enablement for methods of increasing the secretion of any protein, or any HSP/antigen complex, comprising any KDELr ligand using any KDELr inhibitor as recited in Claims 20-37. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 20 is so broad as to encompass methods of increasing the secretion of a protein, wherein the protein comprises any KDELr ligand, using any KDELr inhibitor. Claim 29 is so broad as to encompass methods of increasing the secretion of a HSP/antigenic peptide complex, wherein the HSP comprises any KDELr ligand, and said method uses any KDELr inhibitor. These claims are not enabled in two ways: they are not enabled for a protein or HSP comprising any KDELr ligand and they are not enabled for a method using any KDELr inhibitor.

Although Claims 21-28 and 30-32 are more limited in scope, they are not enabled. Claim 21 is so broad as to encompass methods of increasing the secretion of a protein, wherein the protein comprises any KDELr ligand, using any KDELr inhibitor in which said inhibitor comprises any plurality of protein subunits, wherein each subunit comprises an oligomerization domain and has, at its carboxy terminus, a region which binds to a KDELr. Similarly, Claim 30 is so broad as to encompass methods of increasing the secretion of a HSP/antigen peptide

complex, wherein the HSP comprises any KDELr ligand, using any KDELr inhibitor in which said inhibitor comprises any plurality of protein subunits, wherein each subunit comprises an oligomerization domain and has, at its carboxy terminus, a region which binds to a KDELr.

Claims 22-28 and 31-37 are also not enabled for methods using any KDELr inhibitor comprising any plurality of subunits. Claims 23, 25, 26, 32, 34, and 35 are also not enabled for methods using any KDELr inhibitor in which each subunit has any region, at its C-terminus, that binds to any KDEL receptor. Claims 22 and 31 are also not enabled for any polynucleotide encoding any KDELr inhibitor in which each subunit has any oligomerization domain. Claims 23, 24, 32, and 33 are also not enabled for methods using any KDELr inhibitor in which each subunit has any pentamerization domain. Claims 25, 27, 34, and 36 are also not enabled for methods using any KDELr inhibitor in which each subunit has any pentamerization domain, wherein the pentamerization domain is derived from any cartilage oligomeric matrix protein. Claims 26, 28, 35, and 37 are also not enabled for methods using any KDELr inhibitor in which each subunit has any oligomerization domain, wherein the oligomerization domain is derived from thrombospondin. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of methods of increasing the secretion of a large number of proteins having a large number of KDELr binding domains with said methods using a large number of KDELr inhibitors as broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a secreted protein's amino acid sequence and still have the desired KDELr binding activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of

modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the secreted protein's structure relates to its function. However, in this case the disclosure is limited to the amino acid sequence of KDEL, HDEL, and SEKDEL. Likewise, predictability of which changes can be tolerated in a protein's amino acid sequence and still have the desired KDELr inhibitor activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to the amino acid sequences of SEQ ID NO: 13, 15, 17, 19, 21, 23, 25, 27, 29, and 34 and the nucleotide sequences of SEQ ID NO: 14, 16, 18, 20, 22, 24, 26, 28, 30, and 35.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of:

Claim 20, which encompasses methods of increasing the secretion of a protein, wherein the protein comprises any KDELr ligand and the method uses any KDELr inhibitor.

Claim 29, which encompasses methods of increasing the secretion of a HSP/antigenic peptide complex, wherein the HSP comprises any KDELr ligand, and said method uses any KDELr inhibitor.

Claims 22-28 and 31-37, which encompass methods using any KDELr inhibitor comprising any plurality of subunits.

Claims 23, 25, 26, 32, 34, and 35, which encompass methods using any KDELr inhibitor in which each subunit has any region, at its C-terminus, that binds to any KDEL receptor.

Claims 22 and 31 are also not enabled for any polynucleotide encoding any KDELr inhibitor in which each subunit has any oligomerization domain.

Claims 23, 24, 32, and 33, which encompass methods using any KDELr inhibitor in which each subunit has any pentamerization domain.

Claims 25, 27, 34, and 36, which encompass methods using any KDELr inhibitor in which each subunit has any pentamerization domain, wherein the pentamerization domain is derived from any cartilage oligomeric matrix protein.

Claims 26, 28, 35, and 37, which encompass methods using any KDELr inhibitor in which each subunit has any oligomerization domain, wherein the oligomerization domain is derived from thrombospondin.

The specification does not support the broad scope of Claims 20-37 because the specification does not establish: (A) regions of the secreted protein, or HSP, KDELr binding domain structure which may be modified without effecting the activity of said proteins to bind to KDELrs; (B) regions of the protein structure which may be modified without effecting the activity of the KDELr inhibitors; (C) the general tolerance of the activity of the KDELr

inhibitors to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any residues with an expectation of obtaining the desired biological function; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including (1) any number of secreted proteins and HSPs having a large number of amino acid modifications and (2) KDELr inhibitors with an enormous number of amino acid modifications of the KDELr inhibitors of SEQ ID NO: 13, 15, 17, 19, 21, 23, 25, 27, 29, and 34. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of polynucleotide sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 20-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to methods of increasing the secretion of proteins, and HSP/antigenic peptide complexes, comprising a genus of KDELr binding motifs with said methods using a genus of KDELr inhibitors. The specification teaches the structure of only three

species of KDELr binding motifs and only ten representative species of KDELr inhibitors. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of encoding a protein comprising a KDELr binding motif or a KDELr inhibitor. Given this lack of description of representative species encompassed by the each genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 703-305-1696. The examiner can normally be reached on M-F; 8:30-5 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP 1800